REMARKS

Claims 5, 22, 25-27, 43 and 63-64 have been amended. Claims 13-14, 23-24, 28-29, 36, 51-52, 60-62 have been canceled without prejudice. Claims 1-4, 15-17, 19-21, 38-42, 53-55 and 57-59 have been canceled without prejudice because they are drawn to a non-elected invention. Subsequent to the entry of the present amendment, claims 5-12, 18, 22, 25-27, 30-35, 37, 44-50, 56 and 63-64 are pending and at issue. These amendments and additions add no new matter as the claim language is fully supported by the specification and original claims.

Also, the Examiner has acknowledged that the present application has a valid claim of priority to U.S. Provisional Application No:60/498,906, filed August 29, 2003, which is the effective filing date for purposes of applying prior art.

I. Amendment to the Claims

Claims 5, 22, 25-27, 43 and 63-64 have been amended. Independent claims 5, 22 and 43 claims, have been amended to incorporate aspects of claims 13-14, 51-52, and 60-62, directed to coupling of specific amino acid IL-4 receptor antagonists modifications with a non-protein polymer, and which have been canceled. The amendments are therefore supported by the original claims, as well as the specification (e.g., Examples 5 and 6).

No new matter has been added.

II. Rejections under 35 U.S.C. §112, First Paragraph (enablement)

Claims 5-6, 12-13, 22, 26, 28, 30, 43-44, 50-52 and 60, 62-64 are rejected under on 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one of skill in the art to make or use the invention. Applicants respectfully traverse the rejection as it applies to the pending claims.

According to the Office Action, the claimed invention *is* enabling for a modified IL-4 mutein receptor antagonist coupled to a non-protein polymer at amino acid residue position 37, 38 or 104 and having the amino acid sequence set forth in SEQ ID NO:12-14, wherein the antagonist inhibits stimulation of TF-1 cells induced by IL-4 or IL-13. However, according to the Office Action, the claimed invention is *not* enabling for "all possible" modified IL-4 mutein receptor antagonists having the amino acid sequences set forth in SEQ ID NO:10, 11, 15 or 16 and which inhibit IL-4 and IL-13 mediated activities. In brief, the Office Action alleges that only those antagonists as set forth in SEQ ID NO:12, 13 or 14 and coupled to a non-protein polymer at positions 37, 38 or 104 are enabling. See pages 4-8 of the Office Action.

Claims 5, 22 and 43, and dependent claims therein, have been amended to recite, in part, a modified IL-4 receptor antagonist, whereby the antagonist consists of a cysteine residue at positions 37, 38, or 104 of IL-4, and coupled to a non-protein polymer. This is clearly described in Examples 5 and 6 of the specification. Example 5 describes that "IL4-RE-K37C, IL4-RE-N38C and IL4-20 RE-A104C demonstrated comparable IC_{50} values to that of IL-4-RA in the presence of IL-4 or IL-13 (page 46, lines 19-21)". Example 6 describes that these same constructs when PEGylated "demonstrated an IC_{50} less than 5-fold greater than that of IL-4RA for both primary cell assays (page 47, lines 15-17)". Thus, the claimed invention clearly enables one of ordinary skill in the art to make or use the invention.

With respect to claims 18, 37 and 56, directed to a pharmaceutical composition containing the IL-4 receptor antagonists of claims 5, 22 and 43 and an acceptable carrier, Applicants submit that these claims are enabling as follows. The specification clearly describes methods of making the IL-4 receptor antagonists (Examples 1-3); methods of making various IL-4 receptor antagonist formulations (pages 33-36); methods of administering such to a subject in need thereof (pages 36-39); and methods of determining a therapeutically effective dosage (e.g., page 40, lines 23-28). Thus, the skilled artisan has sufficient guidance to practice the claimed

invention. Further, as stated by the Examiner, the art (e.g., Kips et al. 2001) describes the role of IL-4 and IL-13 in at least asthmatic diseases. The same is described in the present invention, e.g., see the background; page 39, line 10 and 19; and references 1 and 4 on page 49. Hence, the present invention and the art at the time of the filing the present invention are consistent in that both describe that one of ordinary skill in the art could and would predict that the claimed IL-4 receptor antagonist can be used to treat various immunological or allergic disorders.

Accordingly, withdrawal of rejection of claims 5-6, 12-13, 22, 26, 28, 30, 43-44, 50-52 and 60, 62-64 under 35 U.S.C. §112, first paragraph is respectfully requested.

III. Rejections under 35 U.S.C. §102

Claims 5-6, 12-13, 22, 26, 28, 30, 43-44, 50-52 and 60, 62-64 stand rejected under 35 U.S.C. §102(a) as allegedly anticipated by Wild et al (U.S. Patent No. 6,130,318). Applicants respectfully traverse the rejection as it applies to the pending claims.

To anticipate, a single reference must inherently or expressly teach each and every element of claimed invention. *In re Spada*, 15 USPQ2d 1655 (Fed Cir. 1990); and *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). MPEP § 2131. Further, the claimed invention must be distinct from what is apparently inherent in the reference, and the reference must be enabling to place the allegedly disclosed matter in the possession of the public. *In re Fitzgerald et al.*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980); and *Akzo N.V. v. U.S. Int'l Trade Comm'n*, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986).

According to the Office Action, Wild et al. describe human IL-4 mutein protein in which amino acid residues at positions 38 and 105 are modified and coupled to non-protein polymers (i.e. PEGylated).

Claims 5, 22 and 43, and dependent claims therein, have been amended to recite, in part, a modified IL-4 receptor antagonist, whereby the antagonist consists of a cysteine residue at positions 37, 38, or 104 of IL-4, and coupled to a non-protein polymer. Wild et al. does not describe a cysteine at amino acid positions 38 and 105. That is, Wild et al. describe PEGylation of aspartic acid residues at positions 38 and 105 and *not* PEGylation of cysteine residues as 37, 38 or 104 as claimed. Therefore, Wild et al. cannot anticipate the claimed invention because they do *not* disclose *each and every element.*

Accordingly, withdrawal of rejection of claims 5-6, 12-13, 22, 26, 28, 30, 43-44, 50-52 and 60, 62-64 under 35 U.S.C. §102 is respectfully requested.

IV. Rejections under 35 U.S.C. §103

Claims 5-6, 12-13, 22, 26, 28, 30, 43-44, 50-52 and 60, 62-64 stand rejected under 35 U.S.C. §103(a) as being allegedly obvious over Wild et al and Kreitman et al. (1994). Applicants respectfully traverse the rejection as it applies to the pending claims.

To establish a *prima facie* case of obviousness, three basic criteria must be met: 1) a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; 2) a reasonable expectation of success; and 3) the references must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2143.

According to the Office Action, the person of ordinary skill in the art would modify Wild et al., discussed above, to substitute the desired amino acids with cysteine residues as described by Kreitman et al. See page 10 of the Office Action.

It is well established that there must be a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. It is submitted that there is no suggestion or motivation in Wild et al. to replace asparagine with cysteine at positions 38 and 105, because the purpose of replacing asparagine with aspartic acid was to prevent N-glycosylation in the first place (col. 10; line 2). In contrast, the present invention provides cysteine variants because they are "useful when proteins must be refolded into a biologically active conformation (page 15, lines 26-27)". Thus, the purpose of the cysteine mutagenesis of the present invention versus the purpose of the aspartic acid mutagenesis of Wild et al. is for a different purpose. Therefore Wild et al. cannot suggest or motivate the skilled artisan to modify asparagine to a cysteine as alleged by the Office Action.

Kreitman et al. describe a method for coupling *Pseudomonas* exotoxin (PE) to the C-terminus of IL-4 while minimizing the binding impairment of IL-4 to its receptor (Abstract). *Pseudomonas* exotoxin inhibits protein synthesis. For "optimal cytotoxic activity" IL-4 must be fused to the amino terminus of PE and the PE must have a free N- and C-terminus (page 11638, col. 1, first paragraph). Kreitman et al. describe that previous reports have conjugated PE to IL-4 but with decreased affinity (page 11638, col. 1, last sentence of the first paragraph). Thus, the purpose of Kreitman et al. was to develop a site-specific conjugation of IL-4 toxins with improved binding cytotoxic activity. This purpose is distinguished from Wild et al. as well as the present invention. The skilled artisan analyzing both references would not be motivated to mutagenize, e.g., asparagine to cysteine, for the purpose of conjugating it to PE. Conversely, the skilled artisan would not PEGylate cysteine residues of Kreitman et al. because it does not make a toxic IL-4 mutein, which is the purpose of Kreitman et al. Hence, there being no suggestion or motivation to combine the references in the first place, the claimed invention is not rendered obvious in view of the combination of Wild et al. and Kreitman et al.

Accordingly, withdrawal of rejection of claims 5-6, 12-13, 22, 26, 28, 30, 43-44, 50-52 and 60, 62-64 under 35 U.S.C. §103 is respectfully requested.

Conclusion

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

No fee is deemed necessary with the filing of this paper. However if any fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of the Transmittal Sheet is enclosed.

Respectfully submitted,

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